THE DISCOVERY OF INTRAVENOUS UROGRAPHY: HISTORICAL AND DEVELOPMENTAL ASPECTS OF THE UROGRAPHIC MEDIA AND THEIR ROLE IN OTHER DIAGNOSTIC AND THERAPEUTIC AREAS*

The Fourth Ferdinand C. Valentine Memorial Lecture

MOSES SWICK

Consultant in Urology
The Mount Sinai Hospital
New York, N. Y.

I AM deeply appreciative of the honor that you have bestowed on me in presenting me with the Valentine Award. Ferdinand C. Valentine, one of our early pioneer urologists, in whose honor this cherished award has been established, died in the early part of this century. I venture to say that he, with his interest in the furtherance of knowledge, would have been amazed at and delighted with the developments in the field of urology during the past 30 years, particularly in the area of excretion urography with the introduction of the organically bound iodide urographic compounds, which have opened up many new diagnostic and therapeutic avenues in medicine. During Dr. Valentine's lifetime it was possible to obtain very little diagnostic data that enabled one to correct various disorders with a degree of accuracy, especially in the area of pediatric urology. The objectives of the Valentine Award afford opportunities for investigators to continue to contribute to the further scientific progress of urology.

Urography and its clinical application is intimately associated with the development and the investigation of various radiopaque media. For historical purposes, one may consider two separate periods in the development of these media, namely, that of the inorganic iodide radiopaques, administered cystoscopically, and the more recent one, that of the organically bound iodide compounds, administered intravenously,

*Presented at a meeting of the Section on Urology, The New York Academy of Medicine, March 17, 1965.

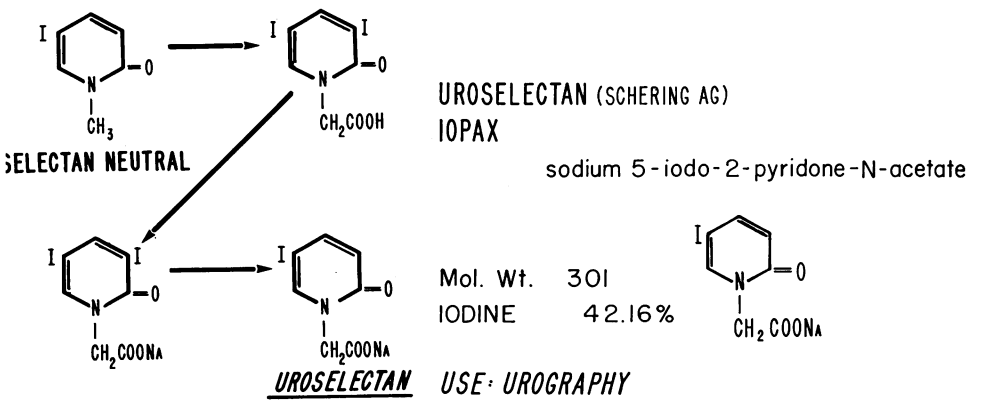


Fig. 1. The structure of Selectan Neutral and Uroselectan.

the latter being responsible for the development of excretion urography and other diagnostic fields in medicine.

On this occasion I shall confine myself to the present era, namely, to the development of the organically bound iodide compounds and their present role in urography.

The organically bound iodides as urographic media were responsible for the successful development of excretion urography. An historical background is therefore not amiss.

In 1923, Rowntree and his co-workers,[1] administering a 10 per cent solution of sodium iodide intravenously and also by mouth, reported the visualization of the urinary bladder and, in some cases, though faintly, the renal pelvis and ureter. Hryntschak,[5] in 1928, employed a series of bromine and iodine compounds identified only by numbers, some of which were aromatic in nature. Roseno,[8] in 1928, used a double compound—sodium iodide-urea. These compounds, as well as all others attempted, fell into disuse because of reactions in some cases; in others, because of the extremely large dose required and the poor results. All the investigators who had utilized the halogen compounds found that these could not be given in sufficient quantities to be of any practical value for excretion urography, though under favorable conditions in occasional cases, the kidney pelvis, calyces, and ureters could be made out.[2-4, 6, 7] A. Roseno stressed the importance of the functional aspects of the problem. In a discussion of Roseno's paper and remarks by

5. NOVEMBER 1929

8. JAHRGANG. Nr. 45

KLINISCHE WOCHENSCHRIFT.

DARSTELLUNG DER NIERE UND HARNWEGE IM RÖNTGENBILD DURCH INTRAVENÖSE EINBRINGUNG EINES NEUEN KONTRASTSTOFFES, DES UROSELECTANS*

Von

Dr. M. SWICK, New York.

Aus der Medizinischen Abteilung des Altonaer Krankenhauses (Prof. Dr. LICHTWITZ) und d. Urol. Abt. des St. Hedwig-Krankenh. in Berlin (Prof. Dr. v. LICHTENBERG).

Das von Prof. BINZ und Dr. RÄTH dargestellte Selectan-Neutral ist in der Medizinischen Abteilung des Altonaer Krankenhauses seit längerer Zeit bei Kokkeninfektionen der verschiedensten Art versucht worden. Therapeutische Erfolge bei Infektionen der Gallenblase und der ableitenden Harnwege legten es nahe, die Ausscheidung zu untersuchen. Es wurde festgestellt, daß diese sowohl durch die Niere als auch in die Galle erfolgt (Dr. ERBACH).

Fig. 2. Title page of the initial article on the use of Uroselectan in urography.[11]

Hryntschak at the Eighth Congress of the German Urological Society in September 1928, reviewing the accomplishments up to that date, von Lichtenberg stated that his experience in this area had been disappointing and that more progress was not likely.[9]

In 1929, I presented papers on my researches and successful development of Uroselectan (in our country called Iopax) for intravenous urography. It may be of interest to recount the thoughts, the steps, and the trials that led to the final satisfactory result.

In 1928, under a Libman Fellowship, I went to work at the Altona Krankenhaus in Hamburg, Germany, where Professor Lichtwitz was using a compound called Selectan-Neutral for the treatment of coccus infections in man. This compound, iodopyridon-methyl, one of a group synthesized by the chemist Professor A. Binz, had previously been used for coccal infections in cows. Since this compound contained iodine (54 per cent), an element known for its roentgenographic properties, it occurred to me that it might be of value in visualizing the urinary tract. I conducted simultaneous chemical excretion determinations, toxicity, and roentgenologic studies. These studies revealed that the compound was promptly excreted in the urine, and that roentgenologic

examinations in the rabbit and human revealed encouraging results in that the kidney parenchyma and urinary bladder could be visualized not infrequently after the intravenous administration of the drug; the renal pelvis and ureter, on the other hand, were for the most part poorly seen. In one case, that of a high occluding ureteral calculus, satisfactory visualization of the upper urinary tract was also demonstrated. Experiments in rabbits revealed that 0.2 g./kg. of body weight was tolerated without demonstrable disturbances. This would be equivalent to approximately 12 g. of substance (6.48 g. of iodine) as the upper limit for an animal weighing 60 kg. In humans considerably less than this amount was used. Marked individual differences in tolerance were noted. Disturbing factors associated with Selectan-Neutral were diplopia, vomiting, nausea, and headache. Oral administration produced similar results. In no case, however, were the symptoms of such a nature as to deter me from continuing with this work. Simultaneous excretion studies limited to quantitative determination of the iodine component revealed that 75 to 80 per cent of the injected iodine was recovered in the urine. The attained results, although not sufficient for practical purposes, pointed to the potential of the methodology and warranted continued investigation. The problem then resolved itself in modifying Selectan-Neutral in order to accomplish the following results:

1) To diminish the toxicity through the substitution of the methyl radical in order to decrease toxicity and thus permit the administration of a larger dose, thereby attaining a higher concentration of the excreted iodine component, a determinant factor for radiologic success. (The observation of double vision led me to the suspicion, at least empirically, that the methyl radical of Selectan-Neutral might be responsible for the toxic manifestations.) The latter thought was the stimulus for continued investigation that led to the ultimate successful outcome.

2) To increase the solubility by means of a substituted radical so that a larger dose could be administered.

3) To increase the iodine content of the molecule.

After carrying out these investigations for about seven months in Hamburg-Altona, I presented the ideas and results with Selectan-Neutral to Professor Binz in Berlin and sought his aid. He subsequently furnished me with two separate di-iodo-pyridon compounds with the methyl radical substituted (Figure 1). On returning to Hamburg,

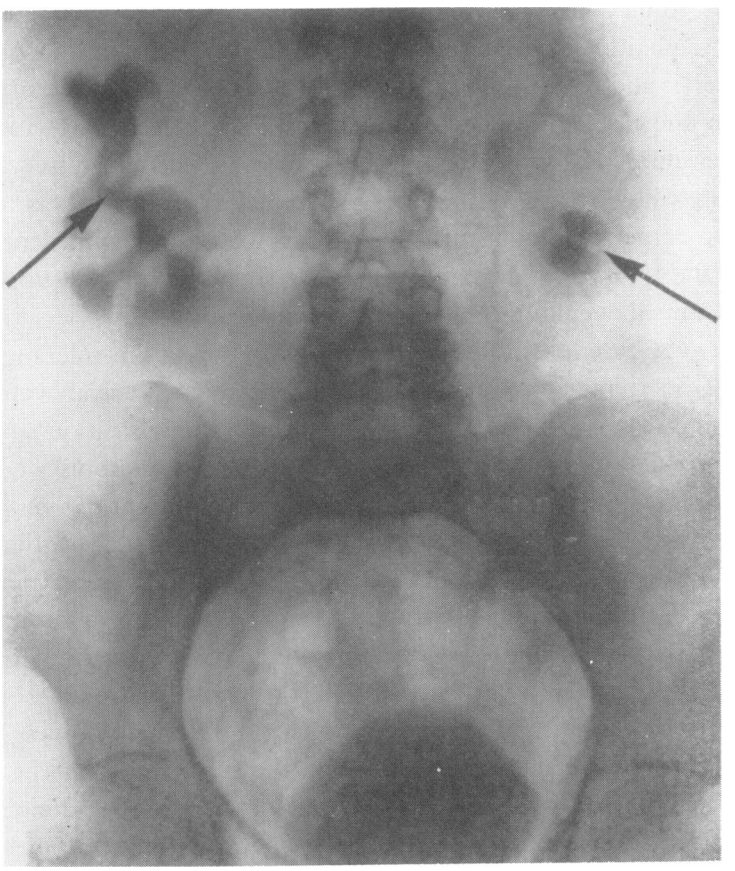


Fig. 3. Figure from the second article on the use of Uroselectan in urography.[11b] The original legend reads: Rechtsseitiger Korallenstein und Harnleiterstein bei 57-jähriger Patientin mit totalem Ausfall der Funktion. Verschärfung des Nierenschattens. Links Steine bloss im untersten Kelch mit guter Darstellung der Harnwege.

both of these compounds, because of their poor solubility, were administered by mouth, not intravenously, to dogs. Neither one was absorbed and both produced x-ray shadows of the intestinal tract.

My investigations were then transferred to the large urological service of Professor von Lichtenberg at the St. Hedwig's Krankenhaus in Berlin. This also afforded me close contact with Professor Binz, who followed these investigations with great interest and was confident that the specifications could readily be fulfilled. Meanwhile, I continued to work with Selectan-Neutral at the St. Hedwig's Krankenhaus awaiting

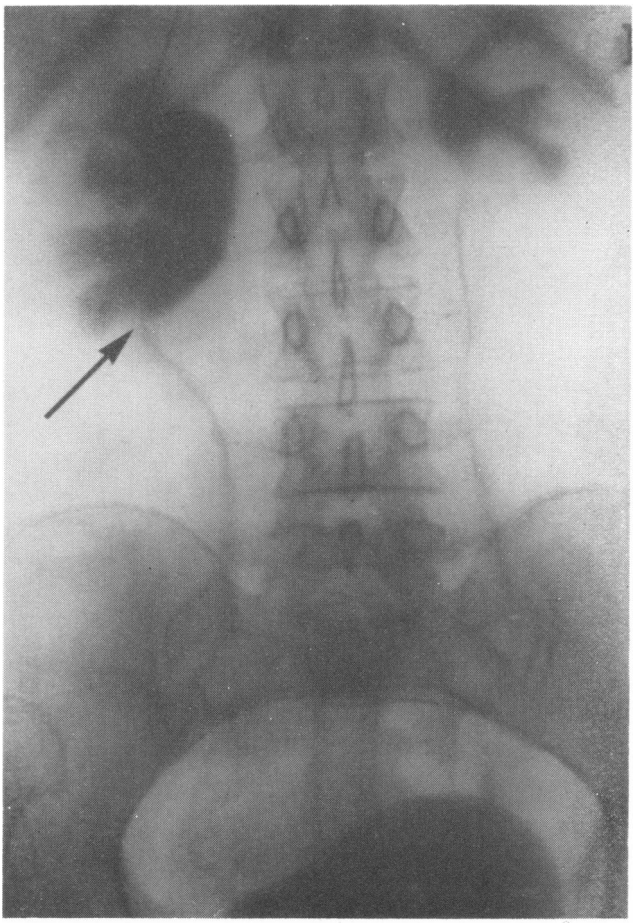


Fig. 4. Figure from the second article on the use of Uroselectan in urography.[11b] The original legend reads: 36jährige Patientin mit rechtsseitiger Verstopfungsniere im Moment der Entleerung dargestellt. Die linke, normale Seite ebenfalls als vollständiges Urogramm zu sehen.

the development of modified compounds with the pyridon nucleus. In order to obtain greater solubility and eliminate toxicity, Professor Binz and Dr. Räth of the agricultural College in Berlin (the Chemical Institute) prepared the modification of the Selectan-Neutral in which the methyl radical was replaced by a sodium acetate radical. Solubility was also increased by lowering the iodine content from the di-iodo-pyridon to the original mono-iodo-pyridon nucleus of Selectan-Neutral. This new preparation, named Uroselectan, fulfilled the necessary

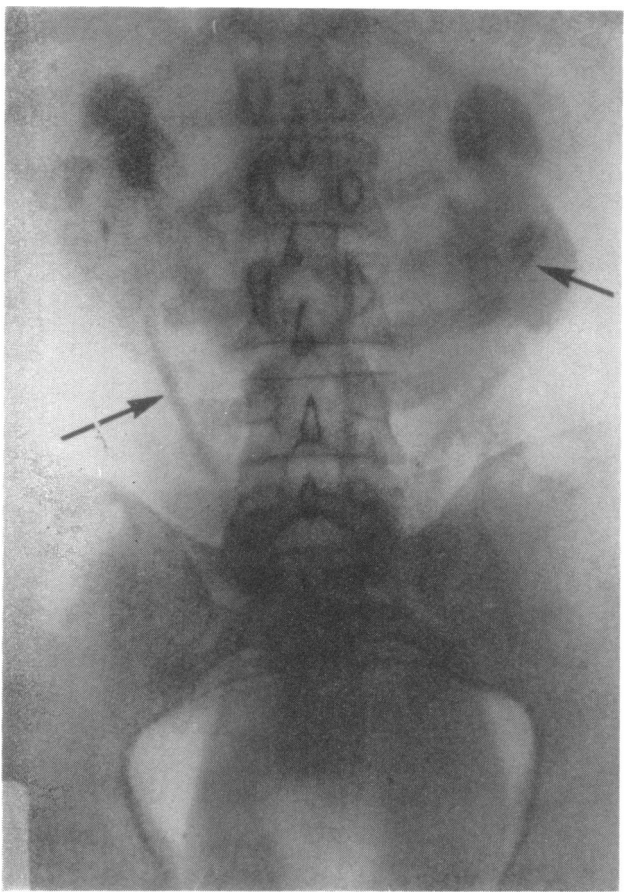


Fig. 5. Figure from the second article on the use of Uroselectan in urography.[11b] The original legend reads: Hufeisenniere bei 36jährigem Mann mit Steinen und wesentlicher Erweiterung beider Nierenbecken. Die abnorm verlaufenden Harnleiter gut sichtbar.

requirements (Figure 1). In 1930 Professor Lichtwitz, at whose clinic my work was initiated, recorded the sequential development of the successful compound.[10]

Uroselectan is nontoxic with the dose used, highly soluble in water, neutral in reaction and, under normal conditions, excreted unchanged through the kidney in sufficiently high concentration to yield good x-ray visualization. Figures 2-5 represent my first roentgenologic successes published in the *Klinische Wochenschrift* in November 1929, and

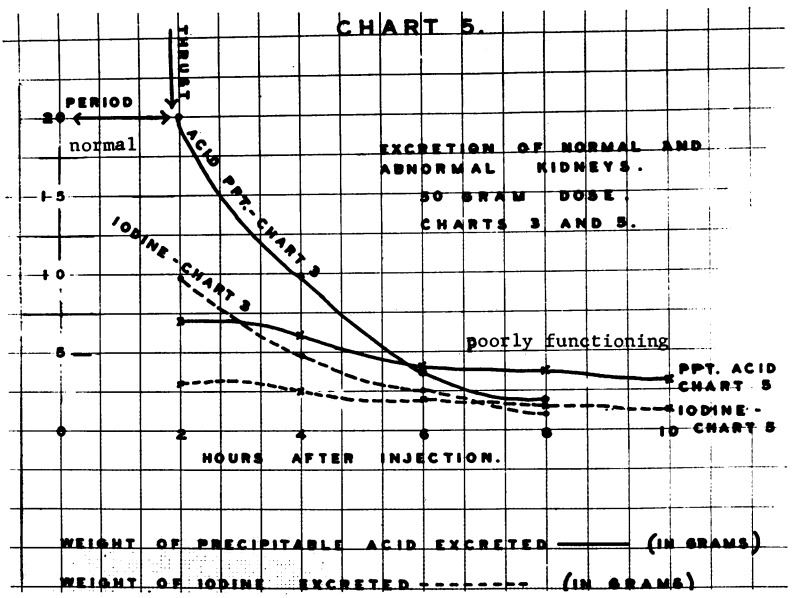


Fig. 6. Curve of excretion of Uroselectan.

in the *Zeitschrift für Urologische Chirurgie*, recording my lecture and presentation before the Ninth Congress of the German Urological Society, held in Munich in September 1929.[11-17]

Uroselectan is well tolerated intravenously. Rabbits could tolerate repeated daily doses of 3 g./kg. of body weight. Using this latter figure as a basis for calculation, a 60-kg. human, theoretically, could receive about 180 g. of the substance. The iodine content of Uroselectan is 42 per cent, corresponding to 75.6 g. of iodine of the above-calculated 180 g. The preparation is more than 50 per cent soluble in water. The large amount of iodine is held in solution in tightly-bound organic form, which is excreted in the urine unchanged. With normal kidney function, 85 to 95 per cent of Uroselectan is excreted in the urine and can be recovered as such. Thus one can conclude that the drug undergoes no degradation in the body and probably no transformation. Quantitative determinations of the excreted substance can form the basis for a gross test of renal function. About three fifths of the substance is excreted during the first two hours, about one fourth during the next, and the remainder during the subsequent several hours.

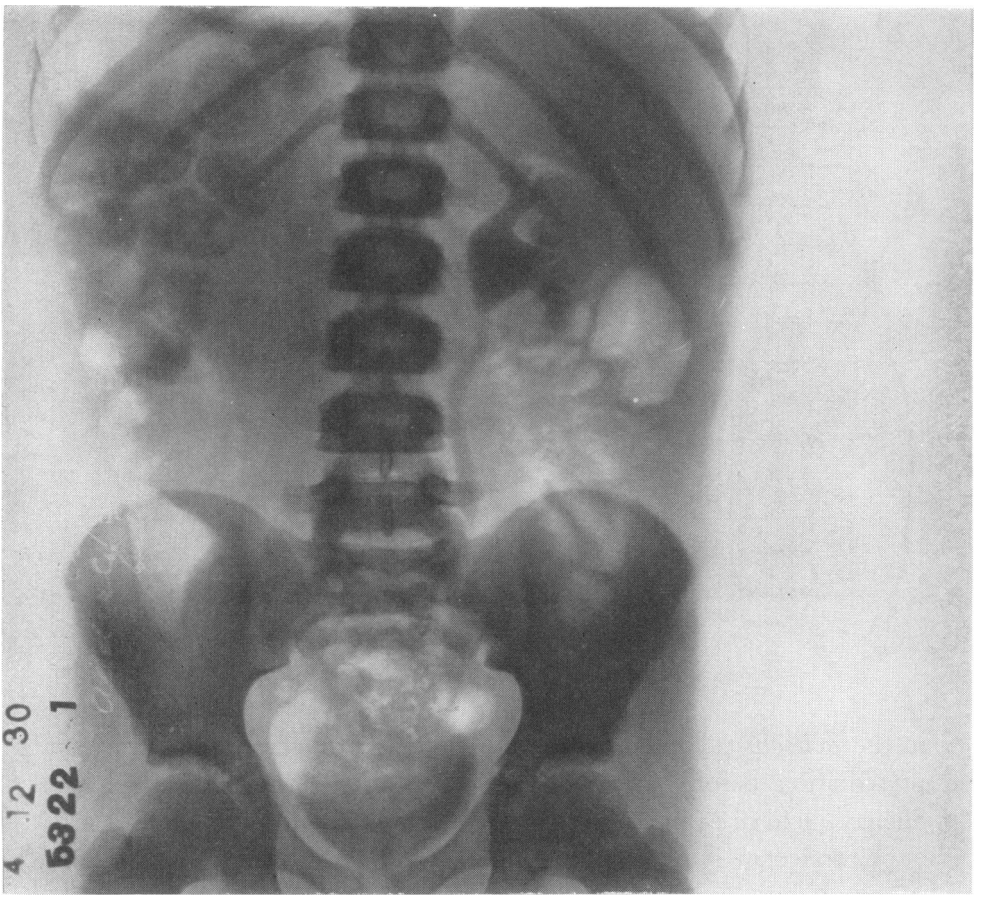


Fig. 7. Intravenous urogram of a boy aged 13, admitted for pyuria and left-loin pain, showing normally appearing and functioning right urinary tract and early filling of several sacculations (dilated calices) of left kidney. Done with Uroselectan. Reproduced by permission of the *Journal of the American Medical Association.*[40]

Permit me to digress for a moment from the main theme of this paper, in order to interpolate a few pertinent observations bearing on renal function as it relates to excretion urography, as they presented themselves during the initial phases of the development and experiences with the excretory urographic media. Facts that may appear obvious today were stepping stones in the development of the concept and in the interpretation of some aspects of excretion urography as it related to renal function. For example, in the early days, nonvisualization in some instances was erroneously interpreted as being due to a non-

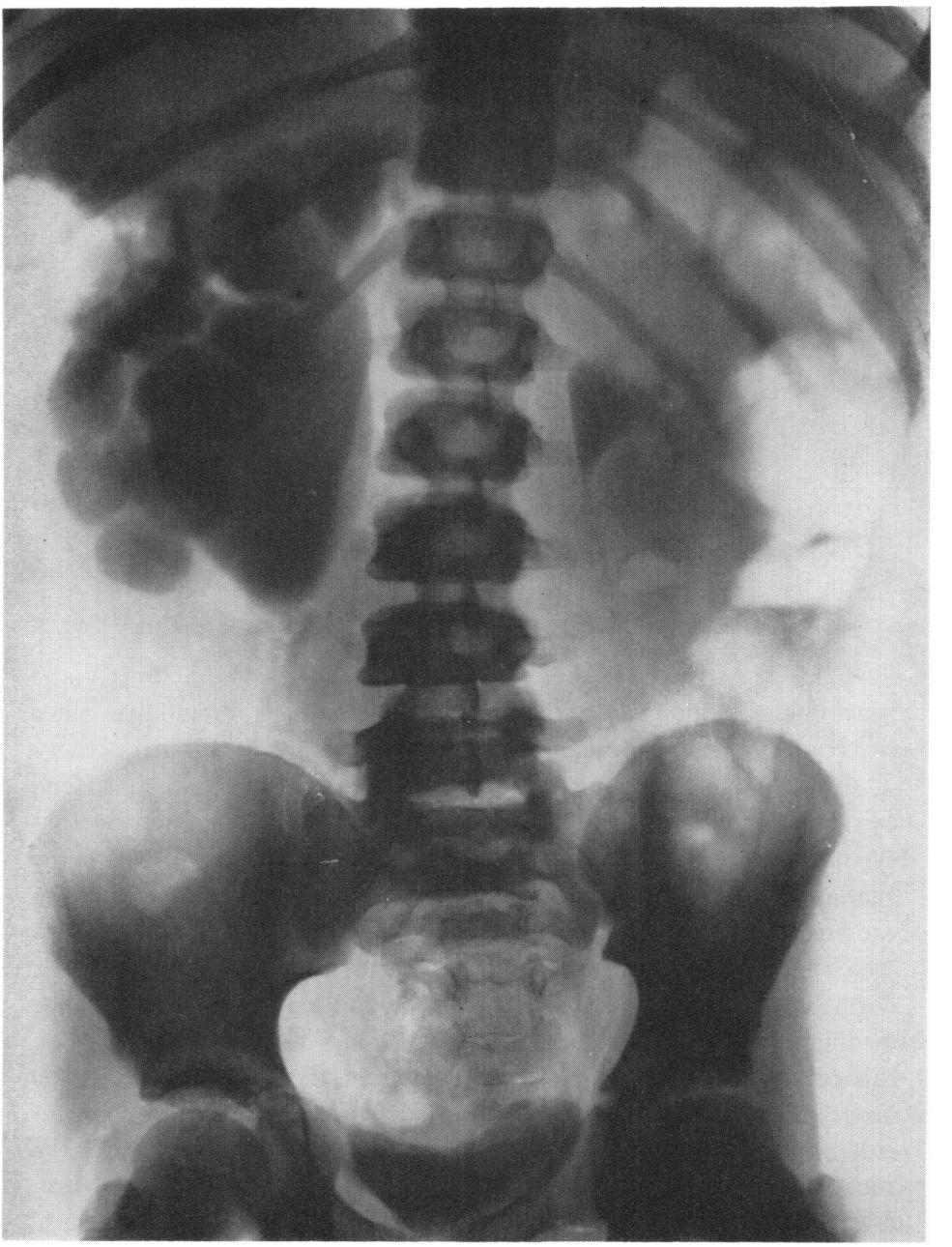


Fig. 8. Same patient as in Figure 7, demonstrating the intense and complete visualization of the left hydronephrotic kidney, obtained several hours after the injection, for practical purposes merely a large hydronephrotic sac. Done with Uroselectan. Reproduced by permission of the *Journal of the American Medical Association.*[40]

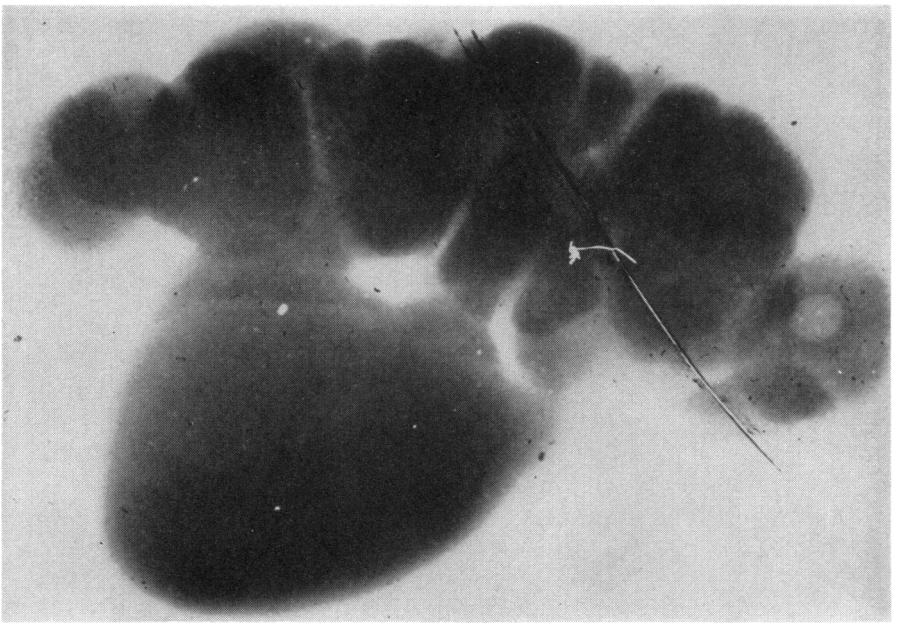


Fig. 9. The injected nephrectomized specimen depicting the huge hydronephrotic sac.

functioning kidney with resultant unnecessary nephrectomy. Since excretion urography depends for its success on the functional activity of the kidney parenchyma, one should be cognizant of the renal and extrarenal factors that determine the net result in that functional activity; only in this manner can one properly interpret and evaluate the anatomic results obtained. The normally functioning kidney is able to excrete urographic substances in high concentration in a short period, which may be characterized as the "thrust-excretion ability of the normally functioning kidney"; roughly, 66 to 70 per cent of the opaque medium is excreted within the first two hours (Figure 6). It is upon this concentrating power of the kidney that the success of excretion urography depends. As a corollary, when this concentrating power is either impaired or absent, as in the poorly functioning kidney, the roentgenologic visualization is correspondingly poor or entirely absent.

Broadly speaking, then, the degree of visualization depends on renal and extrarenal factors that determine renal excretion. However, in the presence of urinary tract obstruction, satisfactory visualization may still take place, although the normal rate of excretion required for roent-

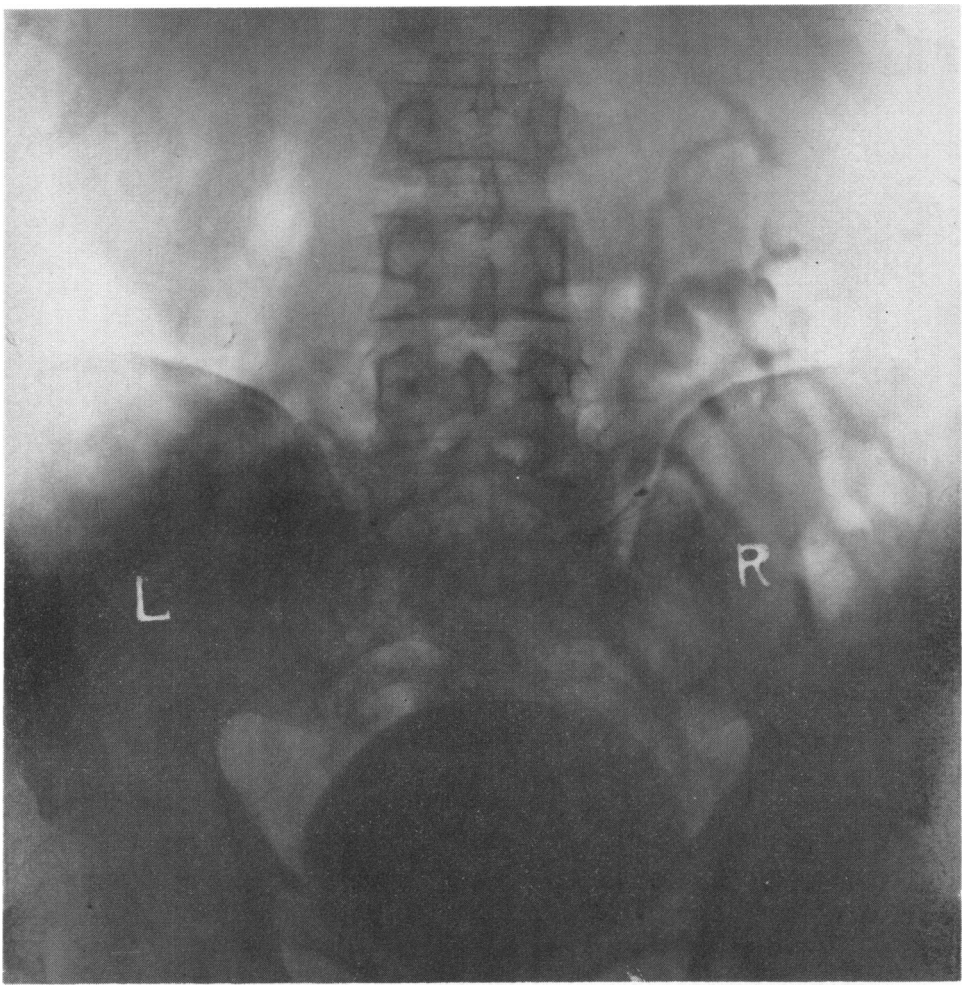


Fig. 10. This demonstrates absence of visualization of the left renal pelvis and ureter with opacification of the previously traumatized side; the double pelvis and forked ureter of the functioning right side is demonstrated.

genologic purposes is impaired, provided that excretion still exists. Thus in cases of hydronephrosis, in which a reservoir mechanism is in effect, good visualization may still be obtained in late roentgenograms despite the existence of relatively little intact functioning renal tissue. An important concept to be derived from case illustrations bearing upon this consideration is the following: that in cases of hydronephrosis the intensity of roentgenologic shadow is not always a quantitative criterion

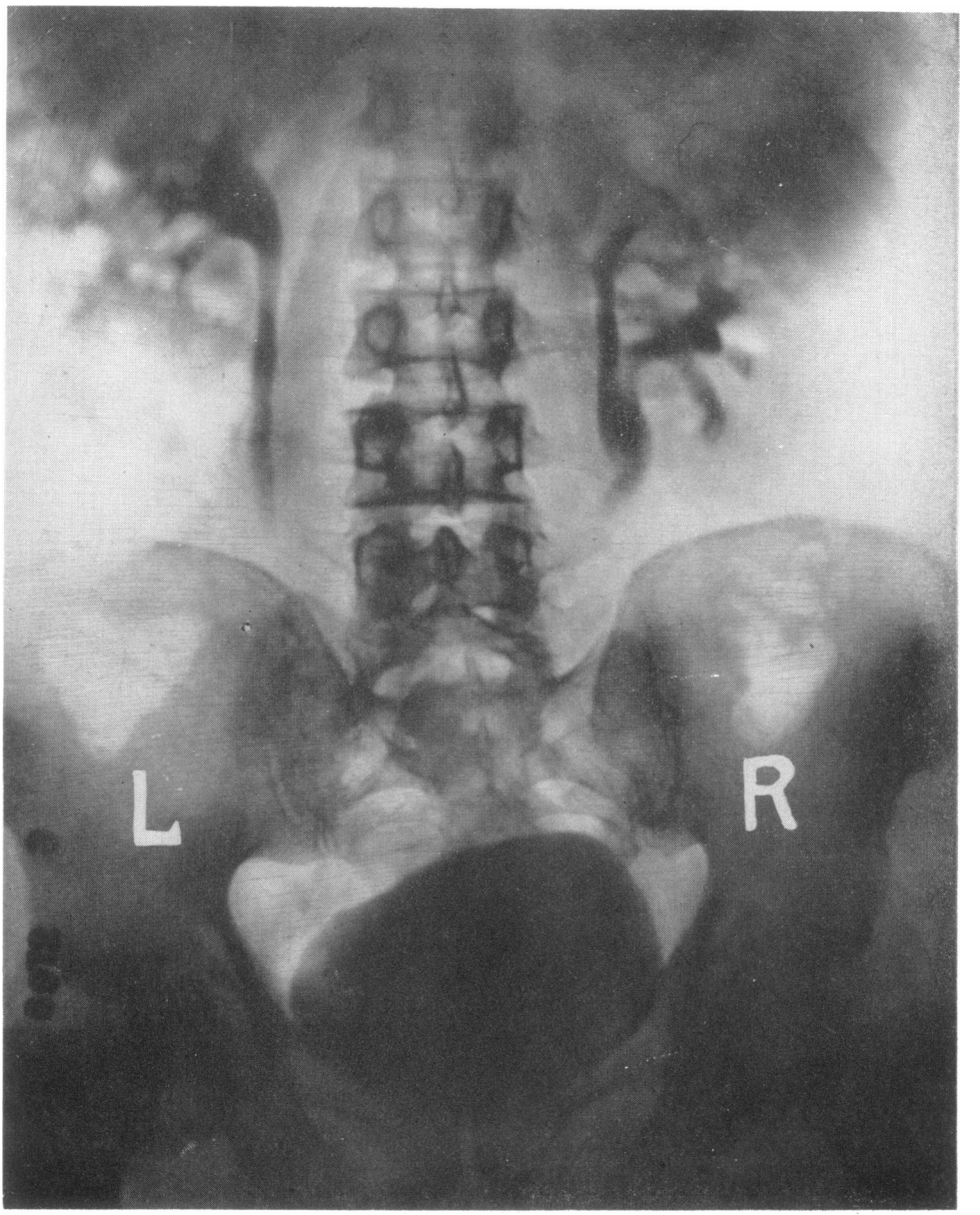


Fig. 11. Subsequent intravenous urographic examination performed three months later now shows the return of function of the left kidney demonstrating a normal left upper urinary tract plus the previous findings on the right side.

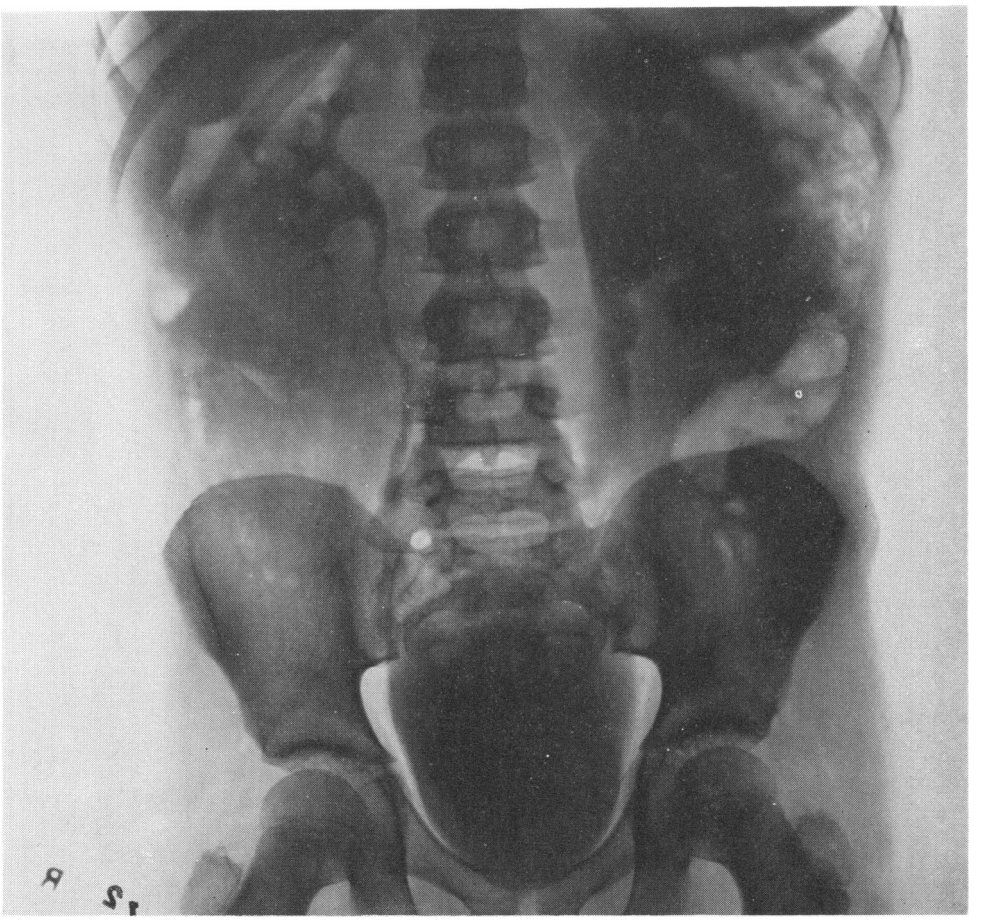


Fig. 12. Marked dilatation of left ureter, kidney pelvis, and calices in a boy age 10, admitted for hematuria. Right urinary tract normal appearing, despite application of compression in midline. (Case of Drs. Leopold and Steward of the Lenox Hill Hospital, New York, N. Y.) Reproduced by permission of the *Journal of the American Medical Association.*[40]

for the amount of intact healthy renal tissue present, nor one for determining the type of therapeutic procedure. The following is an example of this principle:

Figures 7, 8, and 9 demonstrate the intense visualization obtained in a case of a markedly advanced congenital hydronephrosis incidental to an *S*-shaped trapped ureteropelvic junction, even though only comparatively little intact renal tissue was found at operation.

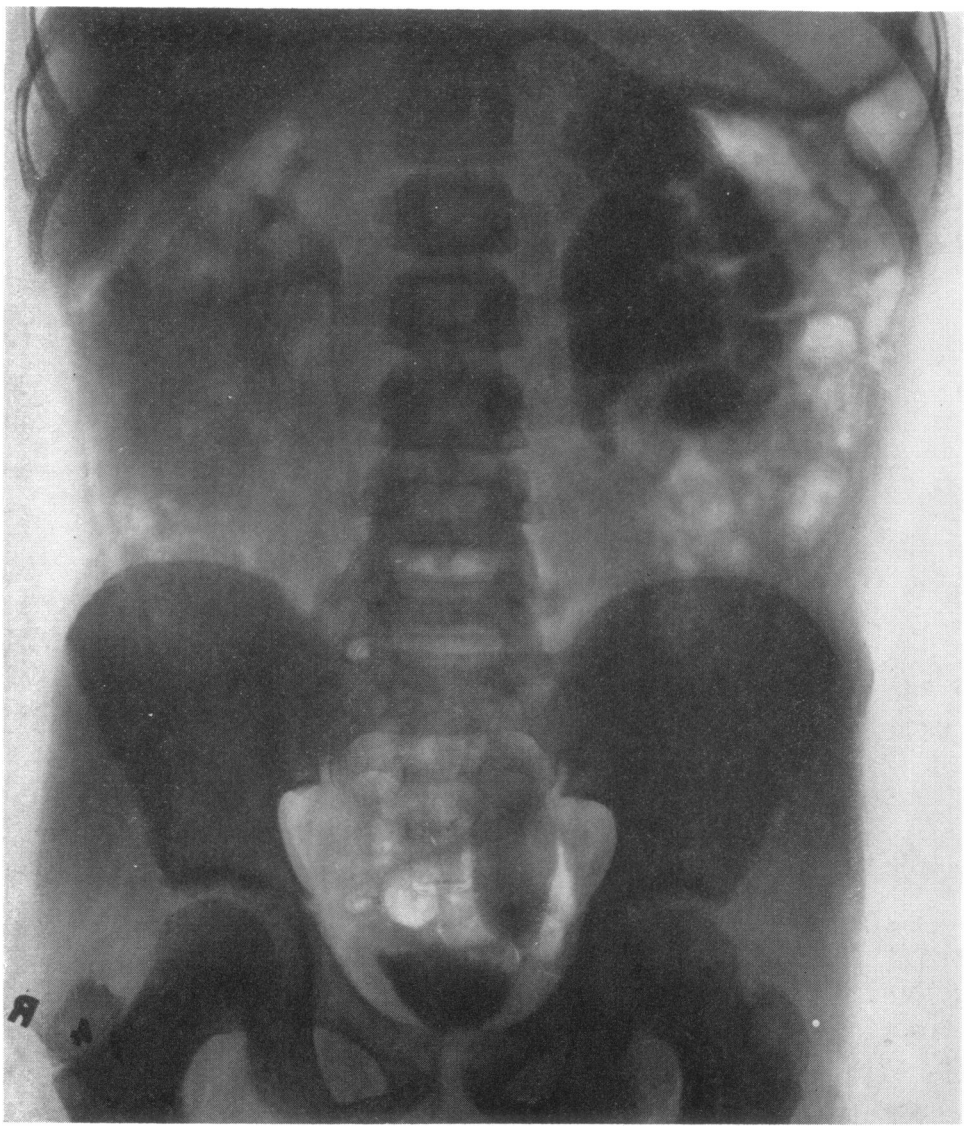
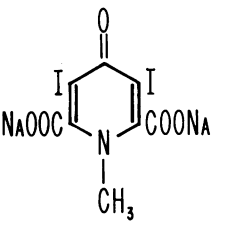


Fig. 13. Same patient as in Figure 12 with bladder partially empty, now demonstrating stricture (congenital) at ureterovesical junction with marked dilatation of lower part of ureter, which was hidden on previous film by distended bladder. Reproduced by permission of the *Journal of the American Medical Association*.[40]

sodium iodomethamate, U.S.P.
iodoxyl, B.P.

disodium 1-methyl-3,5 diiodo-4-pyridone-2,6-dicarboxylate

NEO-IOPAX (SCHERING U.S.A.)
PYELECTAN (GLAXO)
UROPAX (MAY AND BAKER)
UROSELECTAN B (SCHERING AG)
UROTRAST (WELLCOME)



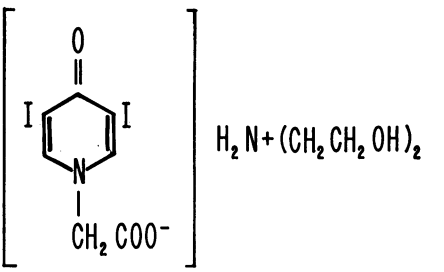
Mol. Wt. 492.9
IODINE 51.5%

USE: UROGRAPHY
ANGIOGRAPHY

iodopyracet, U.S.P.
diodone, B.P.

diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid

DIODRAST (WINTHROP)
NEO TENEBRYL (GUERBET)
NOSYLAN (WINTHROP)
PER ABRODIL (BAYER)
PYELOSIL (GLAXO)
PYELUMBRIN (BOOTS)
UMBRADIL (ASTRA)
VASIODON (MAY AND BAKER)
JODURON (MORPHINE SALT, CILAG)



Mol. Wt. 510
IODINE 49.8%

USE: UROGRAPHY
ANGIOGRAPHY

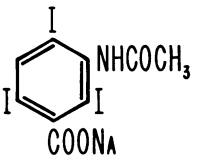
Fig. 14. Chemical formulae of Neoiopax and Diodrast.

Again, the functional activity of the kidney may be temporarily inhibited as a result of either occluding ureteral lesions or trauma, although the kidney parenchyma itself is intact. Under such circumstances opacification of the renal outline is not infrequently observed as a concomitant finding with nonvisualization of the renal pelvis and ureter. The concept of temporary functional inhibition may be valid

sodium acetrizoate

ACETIODONE (GUERBET)
DIAGINOL (MAY AND BAKER)
TRI-ABRODIL (BAYER)
TRIOPAC (CILAG)
UROKON (MALLINCKRODT)

sodium 3-acetamido-2,4,6-triiodo benzoate



Mol. Wt. 478.9
IODINE 65.8%

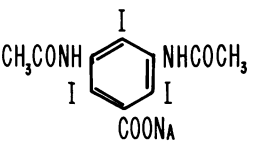
USE: UROGRAPHY
ANGIOGRAPHY

Fig. 15. Chemical formula of Urokon.

sodium diatrizoate

HYPAQUE SODIUM (WINTHROP)

sodium 3,5-diacetamido-2,4,6-triiodo benzoate



Mol. Wt. 636
IODINE 59.87%

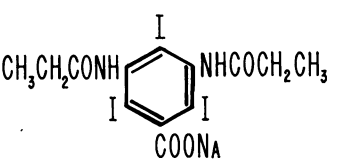
USE: UROGRAPHY
ANGIOGRAPHY

Fig. 16. Chemical formula of Hypaque.

sodium diprotrizoate

MIOKON (MALLINCKRODT)

sodium 3,5-dipropionamido-2,4,6-triiodobenzoate



Mol. Wt. 664
IODINE 57.3%

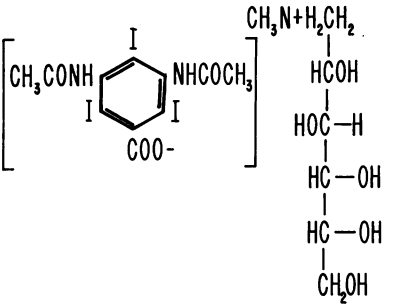
USE: UROGRAPHY
ANGIOGRAPHY

Fig. 17. Chemical formula of Miokon.

methylglucamine diatrizoate

N-methylglucamine salt of 3,5-diacetamido-2,4,6-triiodobenzoate

RENOGRAFIN (SQUIBB)
CARDIOGRAFIN (SQUIBB)



UROGRAFIN (SCHERING AG)
HYPAQUE (WINTHROP)
RENOGRAFIN (SQUIBB)

MIXTURES of the sodium and N-methylglucamine salts of diatrizoic acid

Mol. Wt. 809.2
IODINE 47.6%

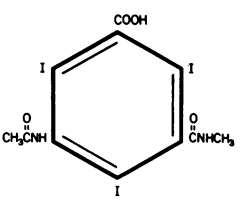
USE: UROGRAPHY – ANGIOGRAPHY.

Fig. 18. Chemical formula of Renografin.

CHEMISTRY

CONRAY® and Angio-CONRAY® are sterile, aqueous solutions of the N-methylglucamine and sodium salts respectively of iothalamic acid.

Iothalamic Acid
(5-acetamido-2,4,6-triiodo-N-methylisophthalamic acid)



Empirical Formula	$C_{11}H_9O_4N_2I_3$
Molecular Weight	614
Iodine Content	62%

CONRAY, the 60% solution of the N-methylglucamine salt, contains 282 mg. of iodine per cc. Its viscosity is 4.0 cps. at 37.5° C. Angio-CONRAY, the 80% solution of the sodium salt, contains 480 mg. of iodine per cc. Its viscosity is 8.4 cps. at 37.5° C. Angio-CONRAY compares most favorably with sodium and methylglucamine diatrizoates 90%, which contains 460 mg. of iodine per cc. and has a viscosity of 21 cps. at 37.5° C.

Fig. 19. Chemical formula of Conray.

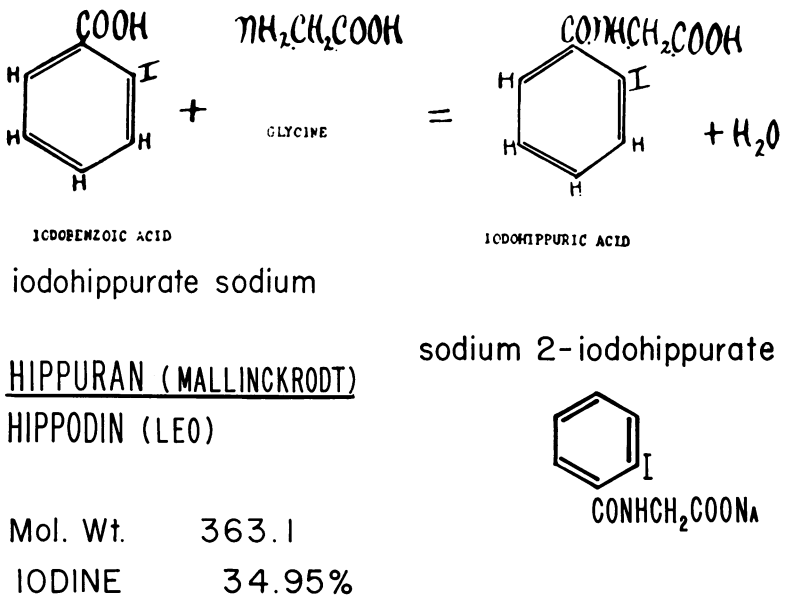


Fig. 20. Chemical formulae of iodobenzoic acid and Hippuran.

in cases with nonvisualization of the urinary tract at one examination, which has been followed by the restoration of renal function with visualization of the urinary tract after the removal of the causative factor. Such experiences have been observed in cases following trauma, and in others from occluding lesions.

Example. A 41-year-old male patient was cystoscoped, and a left retrograde pyelogram was made. At that examination normal indigo carmine excretion from both ureteral orifices was seen. The pyelogram was normal. Following the instrumentation, hematuria and marked pain in the left loin set in and persisted for about a week. When both symptoms had subsided, intravenous urography was done. Absence of visualization of the pelvis and ureter with good kidney outline on the previously pyelogrammed and apparently traumatized left side, in addition to a double pelvis and forked ureter of the right functioning kidney was noted (Figure 10). However, another intravenous urographic examination made about three months later revealed now a normally

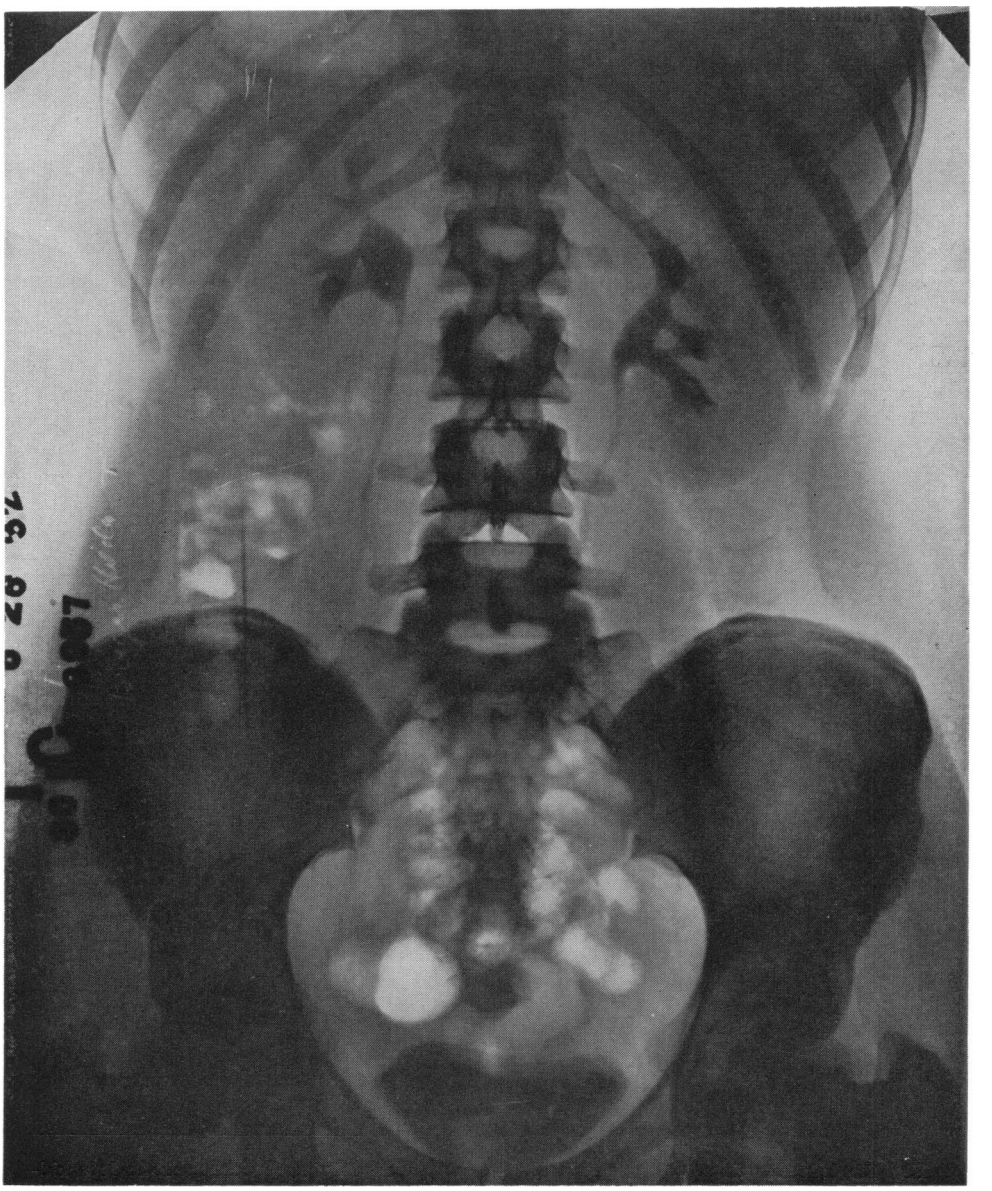


Fig. 21. Intravenous urogram—normal-appearing urinary tracts.

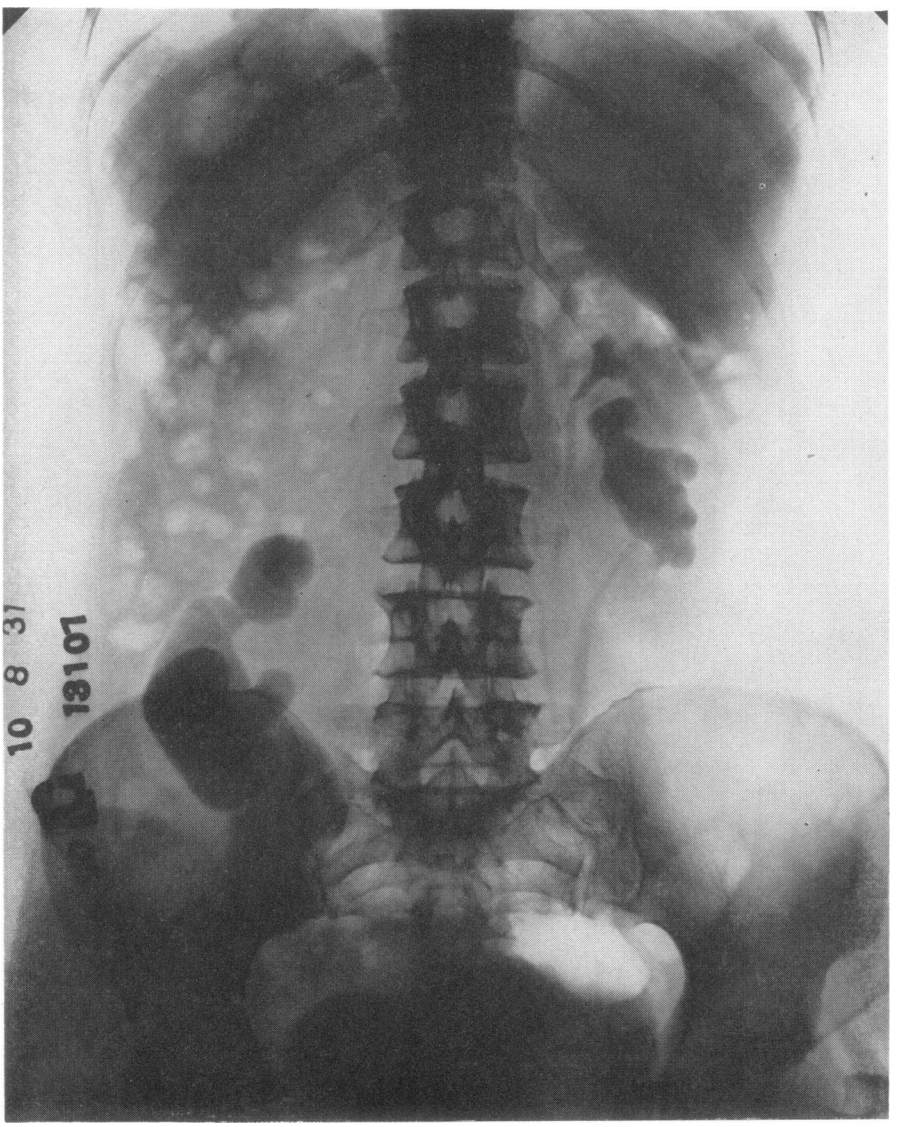


Fig. 22. Intravenous urogram—congenital dystopic nonrotated hydronephrotic left kidney. Double pelvis, double ureter on right side.

functioning and appearing left urinary tract plus the previous findings on the right—a case of temporary functional inhibition following retrograde pyelography. Therefore one should not always conclude that the kidney parenchyma is permanently damaged and beyond repair because of the nonvisualization of the urinary tract at a single examination. As a corollary, very late x-ray films after the intravenous administration of the urographic medium may yield invaluable information following the delayed visualization of the urinary tract in depicting the level of the occluding lesion and the status of the urinary tract (Figures 12 and 13). This case represents the first case I am aware of that demonstrates the contribution of excretion urography in depicting a congenital anomaly in a child, pointing up its potential and role in the further development of pediatric urology.

Returning to the original theme of the paper, the development of two subsequent compounds in Germany was of interest: these, which soon followed upon Uroselectan shortly after my return to the United States, were Neoiopax and Diodrast which, you will note, have a pyridon nucleus similar to that of the original successful Uroselectan[18, 19] (Figure 14). Thus Uroselectan was the forerunner of the above two subsequent related compounds.

In 1931, further investigations of mine led to the formulation of another compound—Hippuran—which I presented and published in 1933. It was based on a metabolic principle differing from the above pyridon substances in that the iodine is organically bound to the 6-carbon-benzoic acid ring instead of the 5-carbon-nitrogen-pyridon ring of Uroselectan. Hippuran, a mono-iodo-benzoic acid derivative, interestingly and importantly bears similarity to our present urographic media, namely, Urokon,[20, 21] Hypaque,[22-26] Miokon,[26-28] Renografin,[25] and Con-Ray[29] in that the latter are tri-iodo-benzoic acid compounds, Hippuran being, as mentioned, a mono-iodo-benzoic acid derivative. A detailed and illuminating treatment of the subject of x-ray contrast media is presented by Dr. James O. Hoppe of the Pharmacology Section, Sterling Winthrop Research Institute, Rensselaer, N. Y.[24, 29a] (Figures 15-19).

Hippuran (38.8 per cent iodine) administered in 50 per cent solution is an iodine derivative of a metabolic product, hippuric acid—normally found in the urine of the horse and man. It is the sodium salt of ortho-iodo-hippurate. It has long been known that the administration

of benzoic acid or iodo-benzoic acid, after the detoxification with the amino acid glycine results in the excretion of the sodium salt of hippuric acid or iodo-hippuric acid (Hippuran) respectively (Figure 20).[30-47] Hippuran satisfies the necessary requirements for excretion urography both by the intravenous and oral routes (Figures 21, 22). Tagged Iodine[131] Hippuran has also been found of value as a test of renal function and a screening diagnostic method by means of the renogram.

In closing, I wish to point out that further important developments from the introduction of the tri-iodo-benzoic acid compounds—Hypaque, Renografin, Con-Ray, etc.—have had *wide application throughout the field of medicine*. For example, their use for *cerebral, cardiovascular, selective renal artery*, and other *local arterial angiographic examinations* have made possible proper localization of lesions for exact surgical approach in their respective fields. These compounds, you will note, are derivatives of the original Hippuran and related to it in that the nucleus of all is the benzoic acid ring. These radiographic organic iodides have made excretion urography the cornerstone of urological diagnostic investigation, lending themselves to studies of the dynamics of the urinary system by ciné-roentgenography, and permitting important information to be obtained from the voiding cystourethrogram, and from nephrotomography. And the end, I hope, is not yet in sight.

REFERENCES

1. Osborne, E. D., Sutherland, C. G., Scholl, A. J., Jr. and Rowntree, L. G., *J.A.M.A. 80*:368, 1923.
2. Rosenstein, P. and von Lichtenberg, A. *Verh. Deutsch. Ges. Urol., 6. Kongress, Berlin, 1924.* Leipzig, Thieme, 1925, pp. 320-21.
3. Volkmann, H. *Deutsch. Med. Wschr. 50:* 1413-14, 1924.
4. Lenarduzzi, G. and Pecco, R. *Arch. Ital. Radiol. 3*:1055-60, 1927.
5. Hryntschak, T. *Verh. Deutsch. Ges. Urol., 8. Kongress, Berlin, 1928.* Publ. as *Z. Urol., Sonderband,* 1929, p. 434.
6. Ziegler, J. and Köhler, H. *Verh. Deutsch. Ges. Urol., 9. Kongress, München, 1929.* Publ. as *Z. Urol., Sonderband,* 1930, pp. 344-345.
7. Ziegler, J. and Köhler, H. *Med. Klin. 26:* 10-11, 1930.
8. Roseno, A. *Verh. Deutsch. Ges. Urol. 8. Kongress, Berlin, 1928.* Publ. as *Z. Urol., Sonderband, 1929,* pp. 431-433. Roseno, A. *Klin. Wschr. 8*:1165-70, 1929. Roseno, A. *Klin. Wschr. 8*:1623, 1929. Roseno, A. *Verh. Deutsch. Ges. Urol., 9. Kongress, München, 1929.* Publ. as *Z. Urol., Sonderband,* 1930, pp. 337-343.
9. Von Lichtenberg, A. *Verh. Deutsch. Ges. Urol. 8. Kongress, Berlin 1928.* Publ. as *Z. Urol., Sonderband,* 1929, p. 435.
10. Lichtwitz, L. *Chirurg. 2.* Jahrg., 1930. Heft *8*:357-61.

11a. Swick, M. *Verh. Deutsch. Ges. Urol. 9. Kongress, München, 1929.* Publ. as *Z.*

Urol., Sonderband, 1930, pp. 328-331;
11b. Swick, M. *Klin. Wschr. 8:*2087-89, 1929.
12. Swick, M. *J.A.M.A. 95:*1403-09, 1930.
13. Swick, M. *Amer. J. Surg. 8:*405-14, 1930.
14. Swick, M. Section on urography, Oxford loose-leaf system, *Surgery 3:*746 (188-3A-48A), 1932.
15. *Medizinische Mitteilungen,* Berlin, Schering-Kahlbaum, February 1930.
16. Von Lichtenberg, A. *Verh. Deutsch. Ges. Urol. 9. Kongress, München, 1929.* Publ. as *Z. Urol., Sonderband, 1930,* pp. 332-336.
17. Von Lichtenberg, A. and Swick, M. *Klin. Wschr. 8:*2089-91, 1929.
18. Von Lichtenberg, A. *Brit. J. Urol. 3:* 119, 1931.
19. Binz, A., Räth, C., Maier-Bode, H. and Herrmann, K. *Angew. Chem. 45:*713, 1932.
20. Wallingford, V. H. *J. Amer. Pharmaceut. Ass. (Sci. Ed.) 42:*721, 1953.
21. Wallingford, V. H., Decker, H. G. and Kruty, M. *J. Amer. Chem. Soc. 74:*4365, 1952.
22. Moore, C., Cloke, B., Hoppe, J. O. and Larsen, A. A. *Amer. Chem. Soc.,* Abstr. 126th Meeting, New York, Sept. 12-17, 1954, p. 11N.
23. Larsen, A. A., Moore, C., Sprague, J., Cloke, B., Moss, J. and Hoppe, J. O. *J. Amer. Chem. Soc. 78:*3210, 1956.
24. Hoppe, J. O., Larsen, H. A. and Coulston, F. *J. Pharmacol. Exp. Ther. 116:* 394, 1956.
25. Langecker, H., Harwart, A. and Junkmann, K. *Naunyn-Schmiedeberg Arch. Exp. Pathol. 222:*584, 1954.
26. Langecker, H., Harwart, A. and Junkmann, K. *Naunyn-Schmeideberg Arch. Exp. Pathol. 220:*195, 1953.
27. Hoffman, A. A., Kocsera, S. J., Portnoy, N. L., Simas, W. and Hastreiter, A. R. *New Eng. J. Med. 255:*343, 1956.
28. Wallingford, A. H. and Turner, R. J. U.S. patent filed July 26, 1954 and approved.
29. U. S. patent issued to George Brooke Hoey, Aug. 18, 1964 (filed 1960). Assigned to Mallinckrodt Chem. Works, St. Louis, Mo.
29a. Hoppe, J. O. *J. Med. Chem. 6:*290-349, 1963.
30. Corfield, C. A. and Mulhuish, B. W. *Chem. Drug 99:*150-52, 1923; *Pharm. J. Pharmacist (4th series) 57:*97-98, 1923.
31. Csonka, F. A. *J. Biol. Chem. 60:*545-77, 1924.
32. Dakin, H. D. *J. Biol. Chem. 6:*103-08, 1909-1910.
33. Griffith, W. H. and Lewis, H. B. *J. Biol. Chem. 57:*1-24, 1923.
34. Lewinski, F. *Arch. Exper. Path. Pharmacol. 58:*397-412, 1908.
35. Lewis, H. B. *J. Biol. Chem. 18:*225, 1914.
36. Novello, N. J., Miriam, S. R. and Sherwin, C. P. *J. Biol. Chem. 67:*555-66, 1926.
37. Raiziss, A. M., Raiziss, G. W. and Ringer, A. I. *J. Biol. Chem. 17:*527-29, 1914.
38. Raiziss, G. W. and Dubin, H. *J. Biol. Chem. 21:*331-43, 1915.
39. Swick, M. *Surg. Gynec. Obstet. 56:*62-65, 1933.
40. Swick, M. *J.A.M.A. 101:*1853-55, 1933.
41. Swick, M. *Radiology 23:*216-22, 1934.
42. Swick, M. *Radiology 26:*539-42, 1936.
43. Swick, M. *J. Mt. Sinai Hosp. 4:*1, 1937.
44. Swick, M. *J. Mt. Sinai Hosp. 4:*6, 1082-91, 1938.
45. Swick, M. The urinary system, in: *An Integrated Practice of Medicine,* vol. 3. London, Philadelphia, Saunders, 1947, pp. 2225-2390.
46. Swick, M. *J. Mt. Sinai Hosp. 14:*821-826, 1947-1948.
47. Swick, M. *J. Mt. Sinai Hosp. 6:*2, 1957.